

HOST PATHOGEN INTERACTIONS: SURVIVAL IN A HOSTILE ENVIRONMENT

I. Introduction:

- A. In order to be a successful pathogen, a microorganism must evolve a system(s) by which it can evade the formidable array of host defense mechanisms available in humans. A wide variety of ingenious mechanisms have been developed by which microbial pathogens persist within human populations. A survey of some of the pathogenic mechanisms of microorganisms will be reviewed in this session.
- B. In the final analysis, all host-pathogen interactions can be summarized in the following simple equation:

$$\text{Probability of infection and disease} = \frac{\text{microbial virulence} \times \text{inoculum size}}{\text{adequacy of host defenses.}}$$

- C. There are four major human defense mechanisms against microbial invasion:
1. Physical barriers - intact integument, mucous membranes.
 2. Nonspecific clearance mechanisms - cough, mucociliary clearance, epithelial cell turnover, GI and GU motility, lysozyme, free fatty acids, lactoferrin, iron sequestering proteins.
 3. Innate Immune Responses: Neutrophils, macrophages, NK cells, alternative complement pathway.
 4. Acquired Immune Response
 - a. Humoral - B cells, plasma cells, Immunoglobulins
 - b. Cellular - macrophages and T cells
- D. In order for a microorganism to cause disease, it must gain access to the host, attach to epithelial membranes, colonize and replicate, avoid nonspecific clearance mechanisms, invade across epithelial barriers, and escape elimination by the humoral immune system, cell-mediated immune system, and phagocytic cell lines. The pathogen must then be able to survive for sufficient length of time to be transmitted to another human host in order to perpetuate itself in human populations. Despite these considerable obstacles, a variety of viral, bacterial and fungal pathogens have adapted to human populations and have become important pathogens in clinical medicine. The fitness of a human pathogen (ability to generate viable offspring) is related to the following equation $R_0 = iDN$ R_0 -fitness; i -infectivity (transmission efficiency x virulence) D -duration; N -number of susceptible contacts.

II. Specific Examples of Successful Human Pathogens:

A. Viral pathogens.

1. Influenza virus - major survival strategies:
 - a. Transmissibility
 - b. Antigenic variation (antigenic drift and antigenic shift).
2. Herpes viruses - CMV, EBV, HSV-1, HSV-2, VZV, HH-6, HH-7, HH-8
Major survival strategies:
 - a. viral latency
 - b. asymptomatic infection and viral shedding thereby maintaining a high prevalence in human populations with continuous exposure to the viruses by susceptible individuals.
3. HIV - The AIDS virus
 - a. antigenic variation - viral envelope
 - b. latency - macrophage, CD4-bearing lymphocytes
 - c. immune destruction - lymphocyte toxicity, super-antigens
4. Example of an unsuccessful viral pathogen:
 - a. Variola (smallpox)
 1. This virus has been eradicated from human populations (extinct) owing to the following characteristics:
 - a. Highly successful vaccine
 - b. Easily identifiable clinical illness
 - c. Obligate human pathogen (no animal reservoir)
 - d. Stable viral genome with little or no antigenic variability
 - e. Relatively long incubation period
 - f. No asymptomatic viral shedding

B. Other viral pathogens potentially susceptible to eradication:

1. polio
2. measles
3. Hepatitis virus A, B, D

C. Examples of successful bacterial pathogens:

1. *Neisseria gonorrhoeae*
 - a. Antigenic variability (pili)
 - b. Antigenic mimicry (LOS similar to myelin components)
 - c. Destruction of immunoglobulin (IgA protease)
 - d. Blocking antibody (non-complement fixing IgA antibody blocks complement fixing IgG antibody attachment).
 - e. clumping - (pili) sharing genetic traits
 - f. porin production - damage WBC membranes
2. *Staphylococcus aureus*
 - a. Adhesins (fibronectin, laminin, fibrinogen)
 - b. Polysaccharide capsule (inhibits phagocytosis)
 - c. Coagulase (stimulates clot formation)
 - d. Catalase (inhibits neutrophil intracellular killing)

- e. Leukocidin (destroys white blood cells)
 - f. Staphylococcal Protein A (fixes Fc fragments of immunoglobulin disrupting correct immunoglobulin attachment and opsonization)
 - g. Antigenic variation
3. *Pseudomonas aeruginosa*
- a. An opportunistic human pathogen, nature habitat is fresh water.
 - 1. Virulence determinants in humans.
 - a. Pseudomonas exotoxin A & S (cellular toxin, inhibits protein synthesis)
 - b. Elastase (destroys immunoglobulin and collagen as well as Elastin)
 - c. Phospholipase C (destroys surfactant, damages cell membranes, releases phosphate)
 - d. Alginate - capsule which disrupts clearance and may impair phagocytosis
 - e. Antigenic variability - pili/and LPS
- D. Examples of a human fungal pathogens
- 1. *Candida albicans* - Ubiquitous and commensal fungal organism which colonizes the human GI and GU tract. Humans are colonized shortly after birth and remain colonized for life. Organism rarely causes disease unless host defenses are altered (neutropenia) or bacterial competitors are eliminated by antibiotics.
 - 2. *Coccidioides immitis*
Coccidioidomycosis represents an accidentally acquired infection in humans. The organism is primarily a saprophytic fungus living in arid soil. Despite the fact that the organism is resistant to phagocytosis by neutrophils and is not limited by humoral immunity, over 95% of patients who inhale *C. immitis* arthrospores do not develop a clinically overt disease. Cell-mediated immunity develops to this organism and eventually eliminates the pathogen. Only severely immunocompromised patients and other special risk groups (pregnant women, people of color) develop disease following infection with *C. immitis*.
- E. Successful Parasitic Infections
- 1. Toxoplasmosis - highly successful protozoan pathogen - large animal reservoir, acts as a commensal organism in most humans; Latency - (tissue cyst); resistant oocyst; infects multiple cell types; lives intracellularly to avoid immune recognition and clearance.
 - 2. Ascariasis - helminthic round worm which lives in the lumen of the intestinal tract. It extracts some nutrients from the host but is generally well tolerated and largely ignored by the host.

SUGGESTED READINGS

1. Relman DA, Falkow S. A molecular perspective of microbial pathogenicity. In Mandell, Douglas and Bennett (editors) Principles and Practice of Infectious Diseases. Churchill Livingstone Publishers, NY 1995. 19-31.
2. Finley BB, Falkow S. Common themes in microbial pathogenicity. Microbiol Rev 1989; 53:21-30.
3. Selander RK, Musser JM. The population genetics of bacterial pathogenesis. In: Iglewski, Clark (editors) Molecular Basis For Microbial Pathogens. Academic Press. Orlando, FL. 1990:11-36.